Section of Urology.

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Chronic Pyelocystitis with Particular Reference to the Ketogenic Diet Treatment.

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(I) Dr. David Band.—*Pathological and Urological Aspects.*

Pathology.—In acute primary pyelonephritis infection may reach the kidney by the blood-stream, or, rarely, by retroperitoneal lymphatic channels. Few specimens of acute pyelonephritis are available for study in the early stages of the condition, but the work of Brewer and others has shown that such a kidney is swollen and congested, and that scattered subcapsular hæmorrhages may be present. In the cortex and in the pyramidal zone minute hæmorrhagic areas are found and the pelvis is congested and œdematous. (Figs. 1 i, ii, iii.) The latter contains an exudate, which is also present in the extra pelvic tissues. The process of repair, moreover, has been shown to be so remarkably efficient that, after resolution, only careful histological examination may reveal minute areas of fibrosis in the renal parenchyma. During resolution the affected areas become sharply localized. A small round-cell accumulation occurs, which may or may not go on to actual abscess formation [1]. (Figs. 2 i, ii.) When resolution is incomplete or repeated infection takes place, secondary abscesses may form leading to suppurative pyelonephritis. (Figs. 3 i, ii.) Repeated mild attacks of pyelonephritis may lead to one type of chronic granular contracted kidney.

Ætiology.—Focal infection throughout the body has been blamed as a source of organismal invasion of the blood-stream. In individual cases the alleged focus has been found present, for example, in the large intestine the site of chronic stasis, in

the retrocæcal appendix, in diverticulitis, in stercoral ulceration of the colon, in the gall-bladder, in the prostate, in the teeth and the tonsils.

Experimentally, acute hæmatogenous pyelonephritis has been produced in laboratory animals by the introduction to the blood-stream of various strains of streptococcus or *Bacillus coli*. It is of note, however, with regard to the colon bacillus that frequently no experimental lesion could be produced by that organism, introduced to the blood-stream, when the kidney was previously undamaged [2, 3 and 4].

That lymphogenous infection of the renal parenchyma and the renal pelvis may occur in a small group of cases is suggested more by clinical observation than by accumulated pathological data, and there is clinical ground for belief that the source of the infection is found frequently in the large intestine, and that the spread has occurred by means of the retroperitoneal lymphatic channels.

When resolution is incomplete in pyelonephritis a chain of events follows which leads to the ultimate destruction of the kidney. (Figs. 4 i, ii.) Inflammatory changes in the musculature of the renal pelvis and calices lead to atony and dilatation which are demonstrable in pyelograms. Stasis leading to residual urine is found in the infected renal pelvis. In a certain number of cases actual inflammatory pelvi-ureteral stricture takes place. (Figs. 5 i, ii.) The researches of Morison [5] demonstrated in the laboratory animal, how, by a process of tubular reabsorption, stasis in the infected renal pelvis leads to widespread dissemination throughout the renal parenchyma, and secondary abscess formation. (Figs. 6 i, ii.) The more virulent the infecting organism the more readily abscess formation occurs. When the infection is milder and more easily overcome there is tubular dilatation alone, followed by interstitial ischæmia and fibrosis. (Figs. 7 i, ii.) Both suppurative pyelonephritis and contracted kidney are equally deficient in functional activity.

Effect on the bladder.—Infection of the bladder from pyelonephritis is a secondary phenomenon. The infection reaches the bladder mucosa by intraluminar spread down the ureter, and on cystoscopic examination congestion, œdema and superficial ulceration are found in the region of the ureteral orifice and on the trigone. As a rule, following resolution of the kidney, the bladder recovers completely, but in cases of more virulent or long-standing infection, extensive ulceration and interstitial cystitis lead to a contracted bladder in persistent systole, a condition which is accompanied by renal backward pressure, and further aids in the dissemination of infection throughout the renal parenchyma.

Pyelonephritis of pregnancy.—Pyelonephritis of pregnancy provides an interesting study in renal infections, worthy of close consideration in comparison with the other types. In pregnancy, stasis in the renal pelvis from dilatation of the upper urinary tract is a constant feature, of varying degrees of severity. When infection is superadded the pathological changes of pyelonephritis follow one another with great rapidity, and often with enhanced severity. This is due to the gross stasis which permits of rapid dissemination of the infection through the renal parenchyma. The dilatation probably arises from the changes in the circulation and innervation of the pelvic organs, including the musculature of the lower ureter, which accompany the pregnant state. (Figs. 9, 10, 11.) Similarly, in the puerperium, pyelocystitis is not uncommon. In a recent publication Rose and Rollins [6] have called attention to the diminished sensitivity of the bladder to contained urine, from compression of, or damage to, the pelvic parasympathetic nerves during labour. The residual urine which collects is specially liable to infection and an ascending renal infection rapidly follows. The prime factor in the renal infections associated with pregnancy is stasis from inefficient urinary drainage. In the simple infections stasis, and inefficient drainage in the urinary tract, are secondary to organismal invasion.

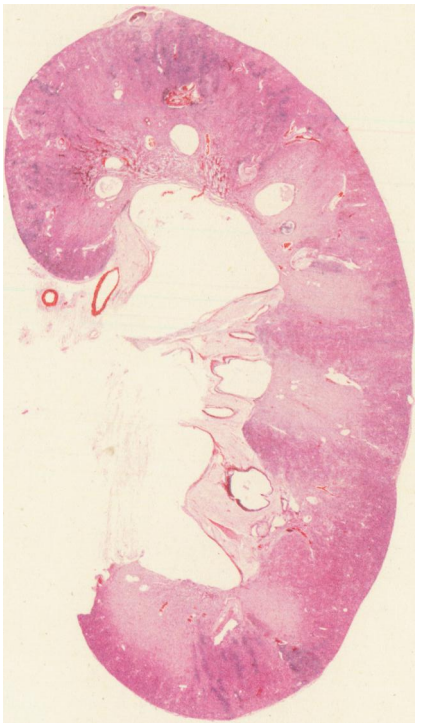


FIG. 1 (i)
Acute hæmatogenous pyelonephritis.

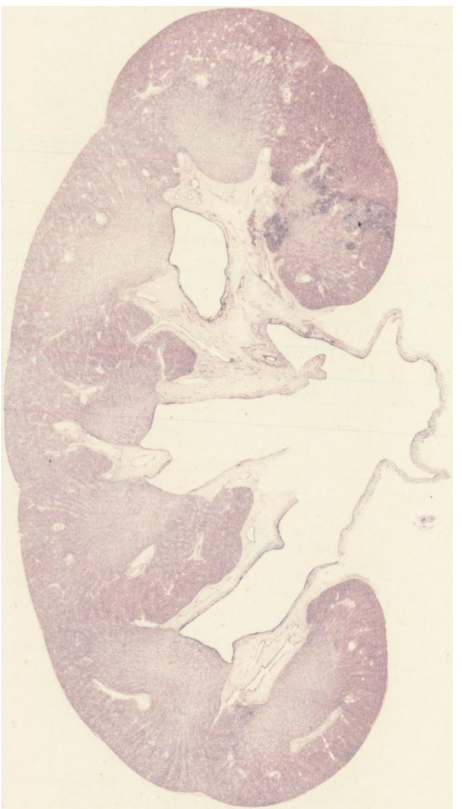


FIG. 8 (i).
Chronic pyelonephritis

PLATE I.

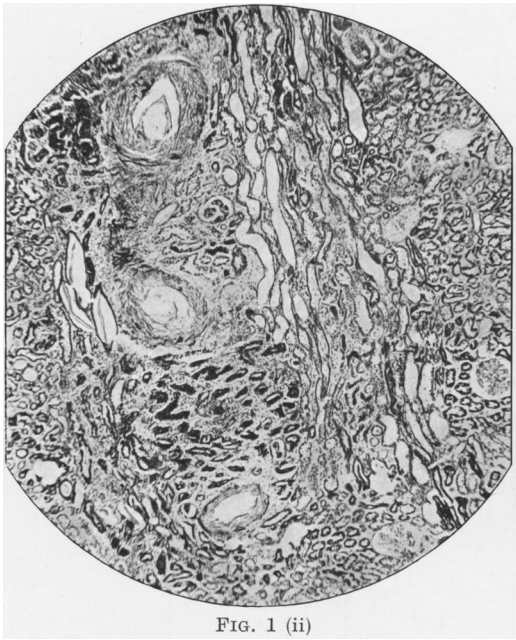


FIG. 1 (ii)

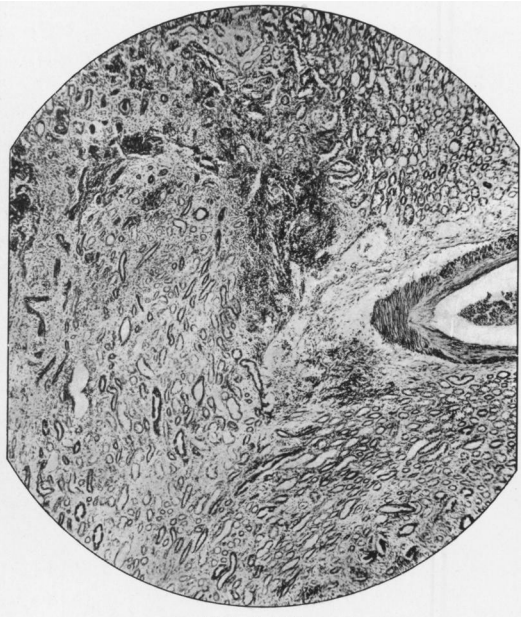


FIG. 1 (iii)

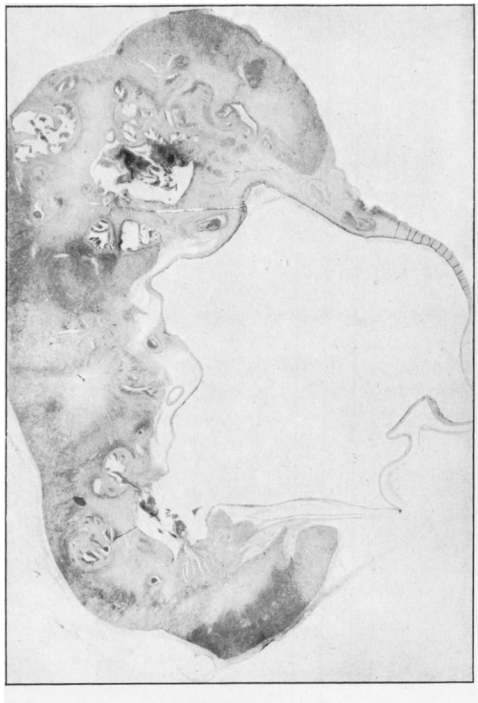


FIG. 2 (i)

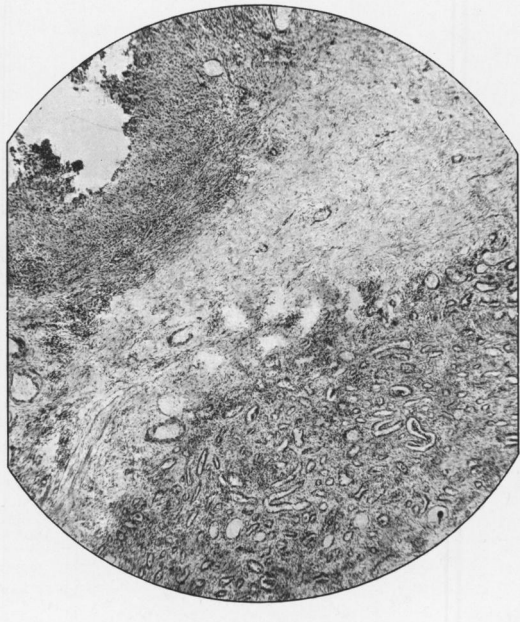


FIG. 2 (ii)

FIG. 1.—(i) Acute hæmatogenous pyelonephritis (see colour plate).
(ii) Necrosis of tubules with round-cell accumulation, thrombosis and fibrosis of glomerulus (× 30).
(iii) Vascular thrombosis (× 30).

FIG. 2.—(i) Suppurative pyelonephritis with multiple abscesses.
(ii) Abscess wall composed of young inflammatory tissue, it is irregular in depth (× 30).

PLATE II.

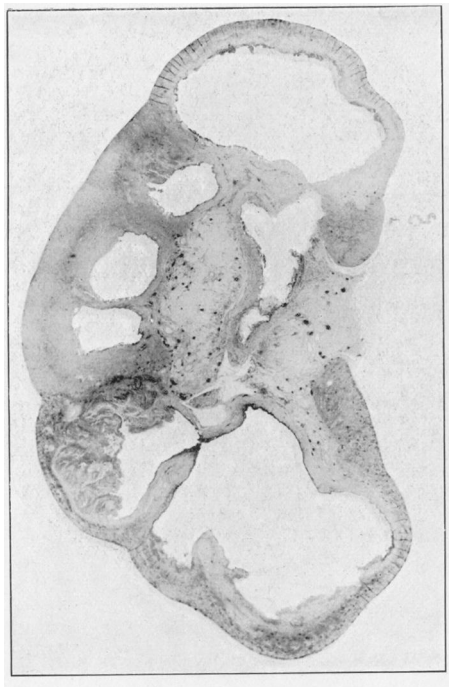


FIG. 3 (i)

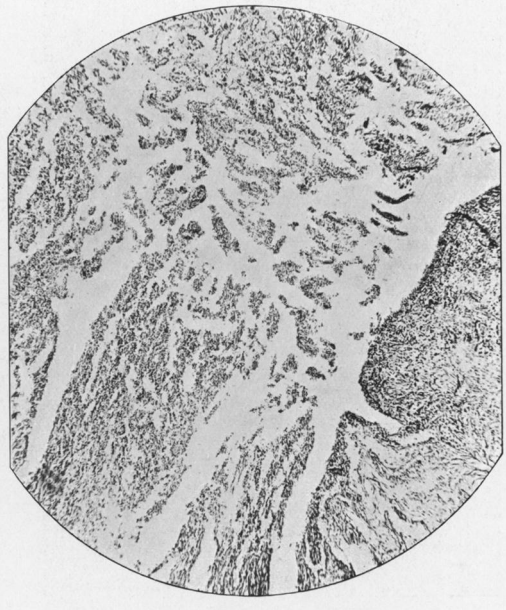


FIG. 3 (ii)

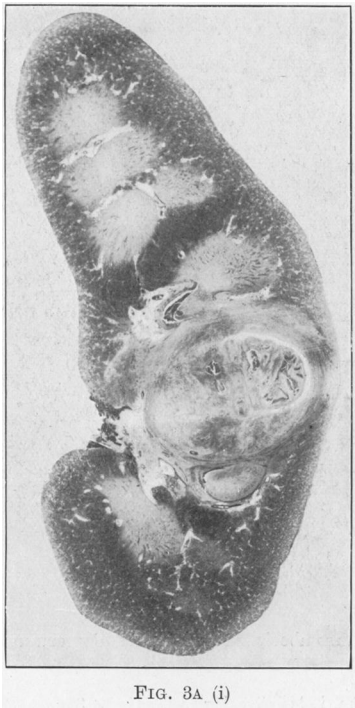


FIG. 3A (i)

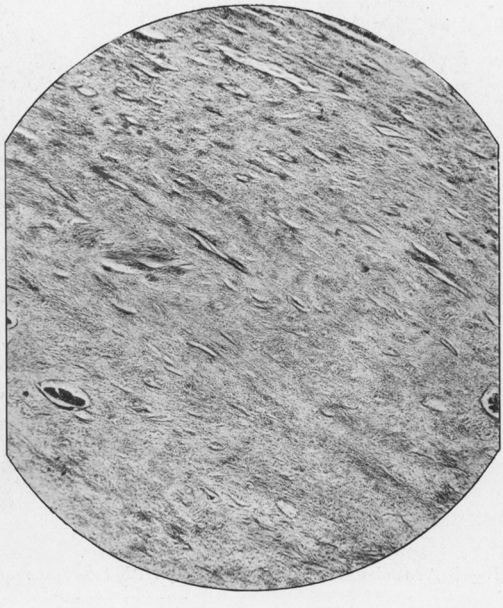


FIG. 3A (ii)

FIG. 3.—(i) Pyonephrosis.
(ii) Abscess cavity adjacent to necrosing parenchyma, absence of fibrous barrier (× 30).

FIG. 3A.—(i) Renal carbuncle (staphylococcal).
(ii) Adult fibrous tissue and sclerosing tubules form a barrier between abscess cavity and healthy parenchyma (× 30).

PLATE III.

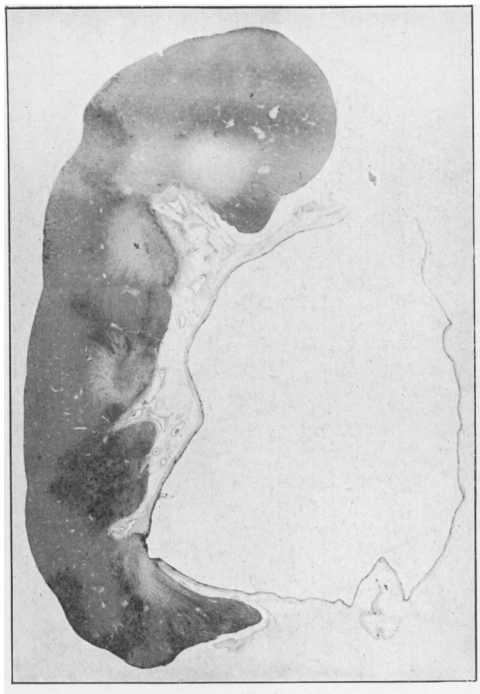


FIG. 4 (i)

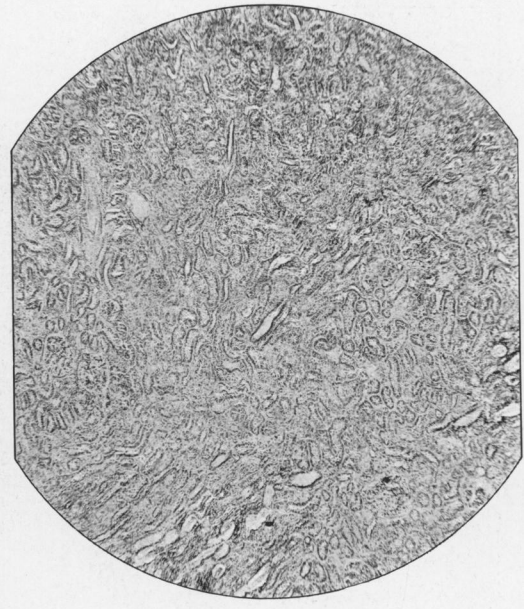


FIG. 4 (ii)

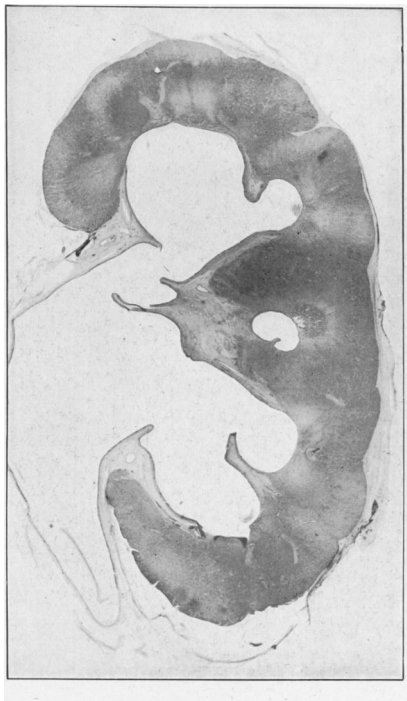


FIG. 5 (i)

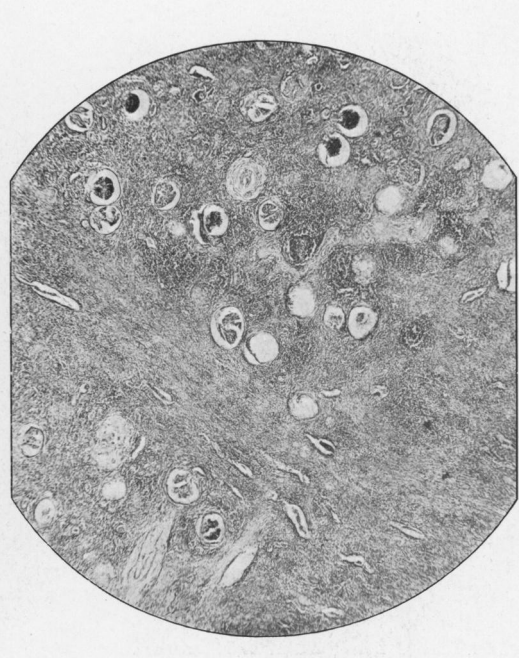


FIG. 5 (ii)

FIG. 4.—(i) Granular contracted kidney secondary to chronic pyelonephritis.
(ii) Minute abscesses scattered throughout parenchyma. Replacement fibrosis of tubules and glomeruli (× 30).

FIG. 5.—(i) Granular contracted kidney—long-standing mild infection.
(ii) Sclerosis and replacement fibrosis of glomeruli and tubules (× 30).

PLATE IV.

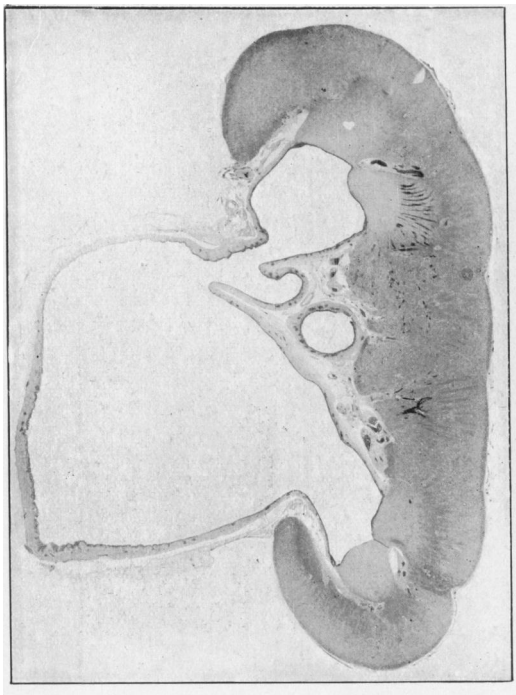


FIG. 6 (i)

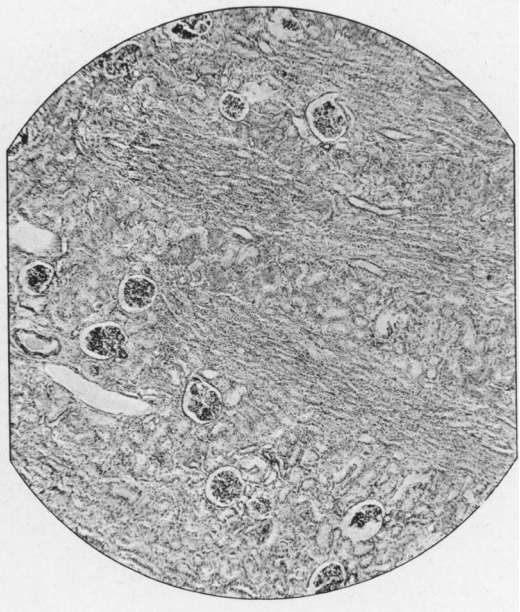


FIG. 6 (ii)

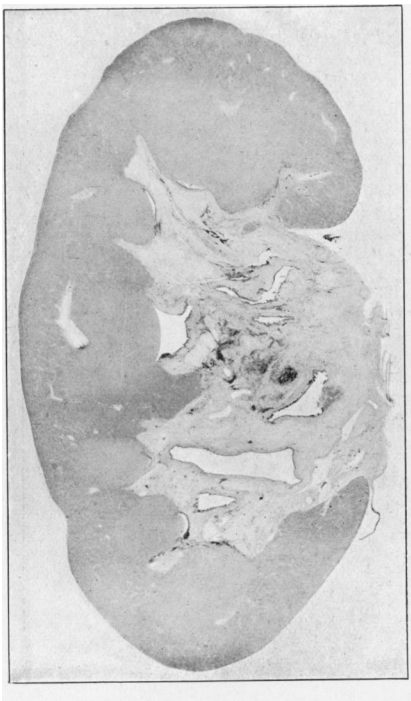


FIG. 7 (i)

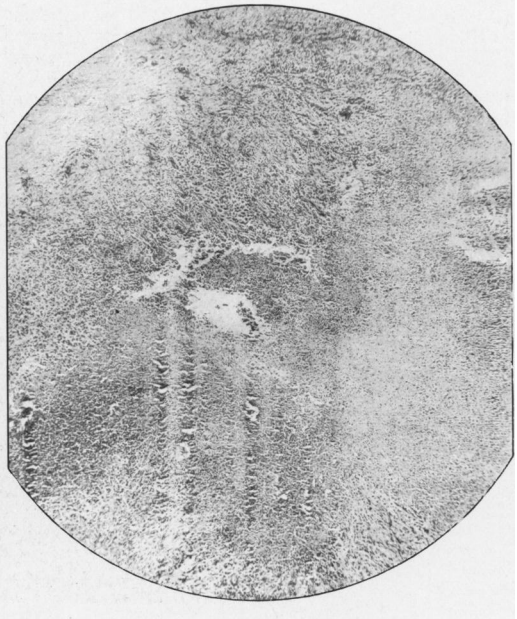


FIG. 7 (ii)

FIG. 6.—(i) Chronic pyelonephritis, cortical abscess (early stage).
(ii) Infection in cortical glomeruli and associated tubules with necrosis (× 30).

FIG. 7.—(i) Chronic pyelonephritis.
(ii) Increase in peripelvic fat and fibrous tissue—round-cell accumulation and early abscess formation in extra-pelvic tissues (× 30).

PLATE V.

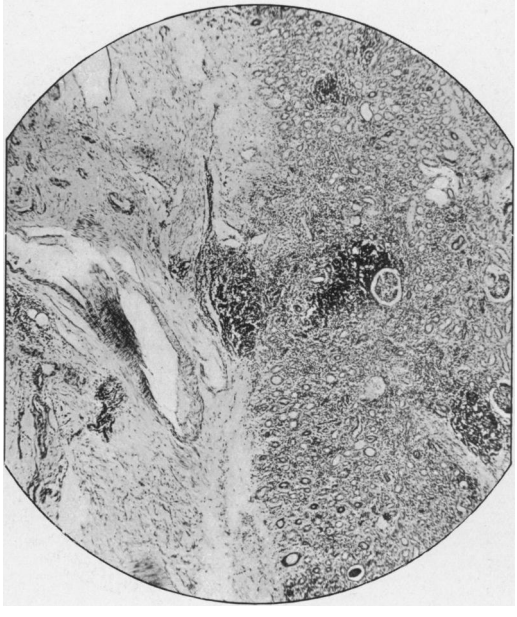


FIG. 8 (ii)

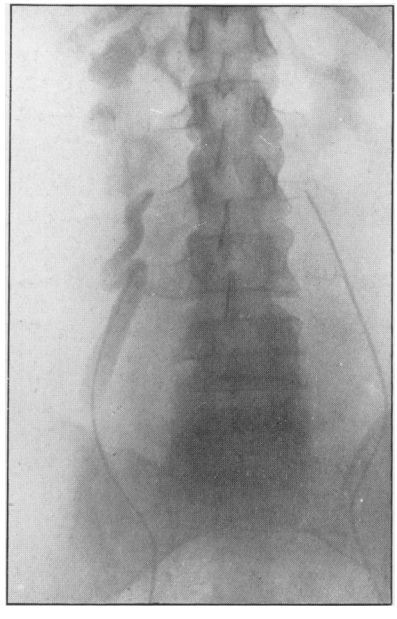


FIG. 9.

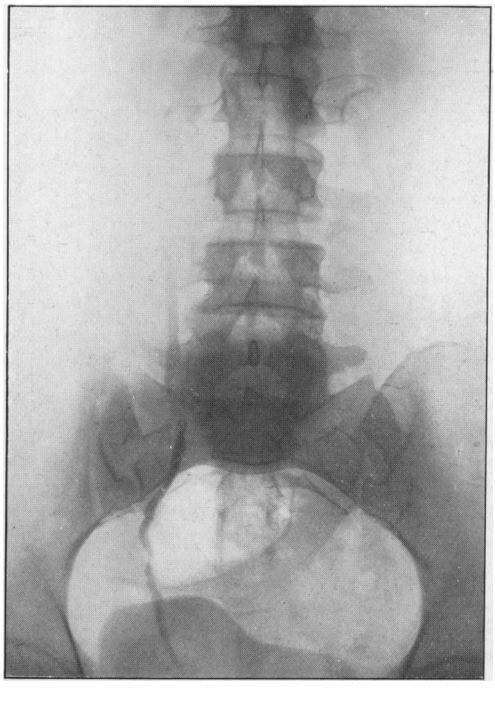


FIG. 10.

FIG. 8.—(i) Chronic pyelonephritis (see colour plate).
(ii) Small round-cell accumulation in parenchyma of kidney communicating with peripelvic fat at the hilum (× 30).

FIG. 9.—Hydronephrosis and hydroureter of pregnancy.

FIG. 10.—Same case after delivery.

PLATE VI.

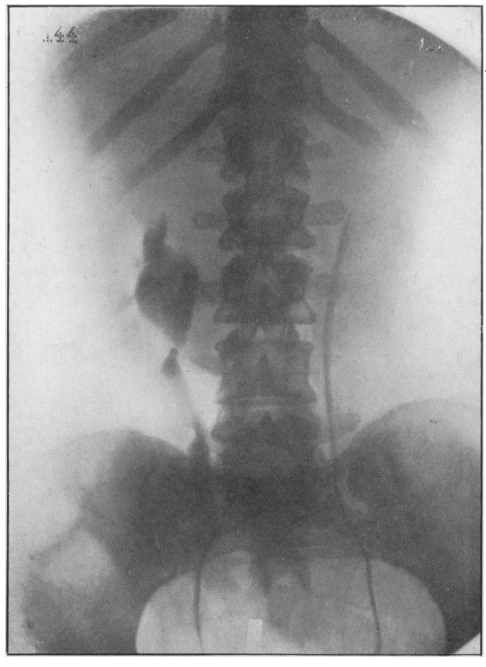


FIG. 11.—Hydroureter and hydronephrosis of pregnancy.

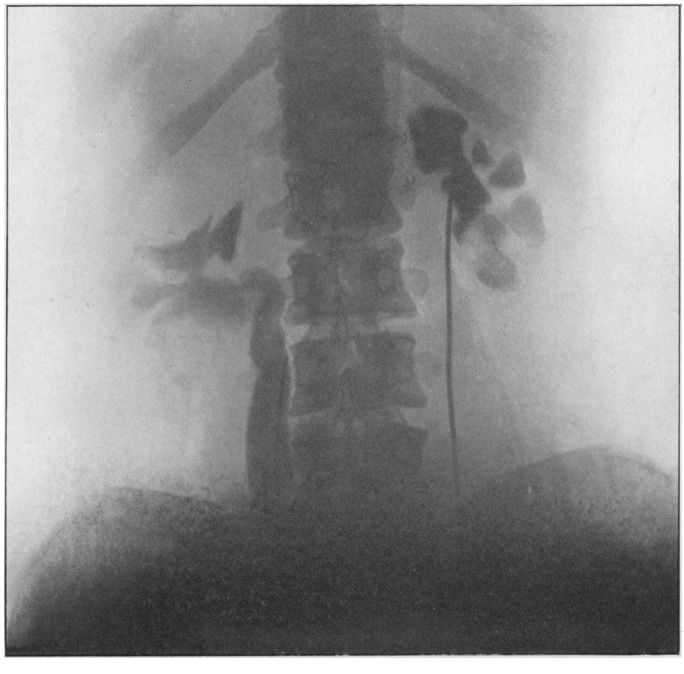


FIG. 14.—Pyelogram of advanced case of pyelocystitis cured by ketogenic diet treatment.

Treatment.—In all infections of the urinary tract the treatment varies according to the stage during which the condition comes under observation. Pathologically speaking, the kidney may be (1) in an acute phase of infection—hyperæmic with recent minute infarcts; (2) relatively destroyed as a functioning organ with numerous abscesses scattered through the parenchyma and gross pelvic dilatation: the pelvis contains frank pus; (3) in a state of chronic infection when the kidney is somewhat hyperæmic and swollen, areas of congestion are present, and scattered points of round-celled accumulation may be found where resolution of an infected area has been incomplete, or where infection has passed from a tubule into the peritubular tissue. (Fig. 8 i, ii.) A few leucocytes only are seen in those areas. The pelvis is moderately dilated and congested. It contains turbid infected urine. The bladder is likewise infected, but the associated vesical lesion may vary from acute simple cystitis to chronic ulceration with systolic contraction.

(1) The treatment of pyelocystitis in the acute stage has always been of the simplest. Abundant bland fluids are administered and diuresis is encouraged by the aid of alkalis.

(2) The treatment of a disorganized kidney is surgical. The decision as to nephrectomy or nephrotomy depends on the state of the opposite kidney and the complications met with in individual cases.

(3) Sub-acute or chronic pyelocystitis cases are notoriously resistant to treatment. It is largely on account of this fact that so many preparations described as urinary antiseptics have been placed on the market. Keeping in mind that the pathological changes ascribed to this group lie within certain limits described above, and that no organic obstruction is present in the urinary tract, the natural lines of attack in treatment are two in number: (1) to increase the bactericidal qualities of the urinary secretion; (2) to encourage and aid the drainage of the renal pelvis.

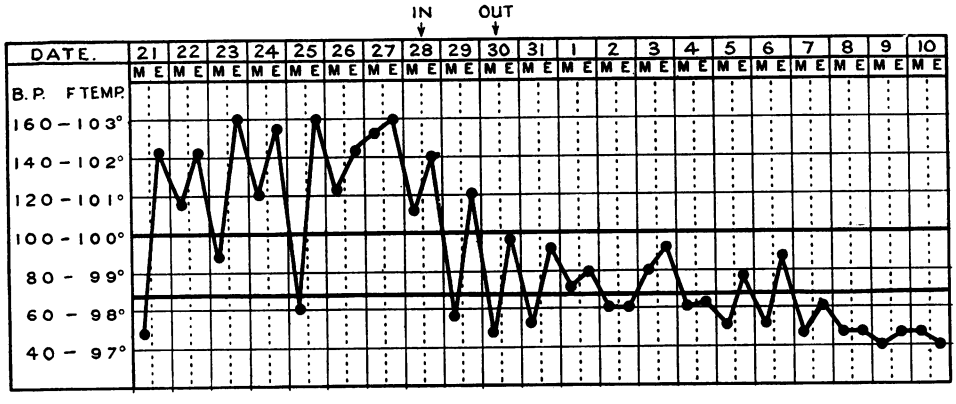
Attention has been drawn to the relative constancy of the pH of urine, and that a highly acid urine is bactericidal. Such a urine is not unduly irritant of itself in the chronic forms of pyelocystitis. Ammonium chloride, calcium chloride, &c., have been found to be well tolerated when given by mouth, and by reducing the pH they act as efficient urinary antiseptics. Diminution of infection in the kidney and in the renal pelvis is encouraged also by the ingestion of large quantities of bland fluids, so that the total urinary output reaches 100 oz. in the twenty-four hours. Attention to the alimentary tract and the location and treatment of focal infections are important therapeutic measures.

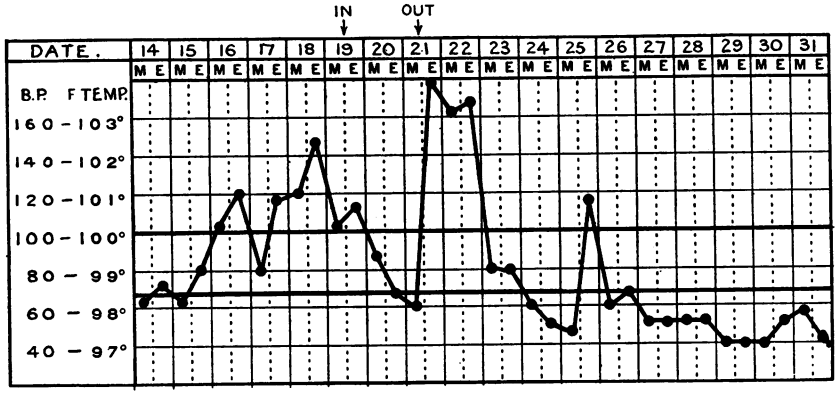
Although emptying of the renal pelvis becomes more efficient as infection decreases, intermittent drainage of the renal pelvis through the ureteral catheter is of the greatest value. Turbid residual urine lying stagnant in the pelvis is thus removed, and the distended wall of the renal pelvis is permitted to contract. Various chemical agents have been advised for local lavage. The salt action of normal saline has much to commend it; the diffusible antiseptics, such as mercurochrome, and the aniline dyes have many adherents, though the chief fault lies in their diffusibility. Silver nitrate has been used up to 2 per cent. strength, which is definitely cauterizing, though in weaker solutions its non-penetration and coagulating effect on the lining epithelium of the renal pelvis render it a safe and powerful antiseptic.

The effect of pituitrin on the contractions of the renal pelvis is uncertain, though there is clinical and experimental evidence [7] that the urinary output may be increased by posterior lobe extract when the urine contains a large percentage of a salt.

The value of simple ureteral catheterization without pelvic lavage is seen most markedly in pyelonephritis of pregnancy, when dilatation and stasis are pronounced features. The therapeutic value of the indwelling ureteral catheter is very great [8],

and by its use alone and in association with urinary antiseptics permanent relief may be obtained. (Figs. 12 and 13.) By the effect of ureteral catheterization, primary pyelonephritis in pregnancy may be distinguished from pyelonephritis secondary to a toxæmia when it is usually necessary to terminate the gestation by emptying the uterus [9].





FIGS. 12 and 13.—Charts of pyelonephritis of pregnancy treated by indwelling ureteral catheter.

In the course of the urological investigation of 3,000 cases with symptoms referable to the urinary tract (excluding venereal disease), uncomplicated infection was found to be present in 400 patients. These investigations were carried out in the Diagnostic Theatre of the Royal Infirmary, Edinburgh, under the direction of Mr. Henry Wade. In 136 cases of chronic pyelocystitis, the patients were kept under observation during treatment, and afterwards they were "followed up" for some years.

In the accompanying statistical tables it is seen that when an analysis is made the data obtained are very similar to those furnished by other hospitals. Following the introduction of the ketogenic diet treatment at the Mayo Clinic, it was arranged to try out this new form of treatment in a series of cases in the "intractable" group which had formed 16·9% of our cases of chronic pyelocystitis.

PYELOCYSTITIS. 136 CASES.

Nature of Infection.

B. coli	Mixed	Streptococcal
104	21	11
or	or	or
76·3%	15·4%	8·8%

Sex Incidence and Average duration of Symptoms.

Male	Female	Years
29	107	1·8
or	or	
21·3%	78·6%	

Symptomatology.

Pain			Frequency	Hæmaturia	Pyuria
L. Kidney	R. Kidney	Nil.			
48	54	34	130	41	136
or	or	or	or	or	or
35·2%	39·7%	25%	99%	30·1%	100%

Analysis of 136 Cases.

Cured	Improved	I.S.Q.
65	48	23
or	or	or
47·7%	35·2%	16·9%

↓

80% slight residual renal pain only.

Dr. Dunlop in the next section of this paper will describe the management and biochemical aspects of the ketogenic diet. From observation of these "intractable" cases during and after this form of treatment there is no doubt of its efficacy. In a revised statistical analysis the number of patients likely to remain in the "intractable" group has fallen to 5 or 6% (fig. 14).

I have to acknowledge gratefully the facilities for the study of pathological material kindly offered by Professor Wilkie in the Department of Surgery, University of Edinburgh, and the skill exercised by the technical assistants of that department in the preparation of the whole sections of kidney specimens.

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(II) Dr. D. M. Dunlop.—*The Ketogenic Treatment of Chronic Pyelocystitis.*

The medical treatment of acute and sub-acute urinary infections consists largely in the administration either of massive doses of alkalies, or of a urinary antiseptic such as hexamine, usually along with acid sodium phosphate. In such conditions

either treatment is frequently successful. An infected urine becomes less irritating to pass when made alkaline; and in addition the diuresis produced by potassium citrate, combined with the diuretic effect of a large fluid intake, with which any treatment is always combined, may mechanically flush clean the urinary tract. It is very doubtful, however, whether alkalies exercise any specific sterilizing effect in virtue of their alkalizing properties, for *B. coli* and other organisms flourish admirably in a urine whose alkalinity, as indicated by the pH, is as great as 9, which is the maximum alkalinity achieved by the therapeutic administration of alkalies. Again, it may be questioned whether oral administration of urinary antiseptics in non-toxic doses ever achieves a concentration of the antiseptic in the urine sufficient to have a significant sterilizing effect. Cases of acute and sub-acute infection, however, usually recover spontaneously, and again, the large quantity of fluid given as a part of the treatment may affect the condition favourably, the antiseptic reaping the credit.

Whatever the view be, however, as to the success of these therapeutic measures in acute and sub-acute infections, opinion must be largely unanimous in recognizing their comparative inefficiency in the chronic type of urinary infection, which Dr. Band has described, and he has confessed that local lavage and other surgical measures may, on occasion, give equally disappointing results in the treatment of such conditions.

B. coli grow well in urine with a pH ranging from 5 to 9. Below and above these limits their growth is to a greater or less extent inhibited. Since it is almost impossible to obtain a pH of greater alkalinity than 9 by the administration of alkalies, several workers have, in recent years, attempted to secure sterilization by the production of a very acid urine. Acid sodium phosphate is inefficient in this respect for, though it will cause an alkaline urine to become acid, it will not cause an already acid urine to become much more acid. In consequence, they have had recourse to acid-forming salts, such as ammonium chloride, ammonium nitrate and ammonium benzoate, and have frequently combined these with hexamine. We have had some experience of this form of treatment in Professor Murray Lyon's department of the Edinburgh Royal Infirmary, and there is no doubt that in this way the acidity of the urine can be markedly raised, though seldom higher than a pH of 5. The results, however, though sometimes successful, are inconstant, and a great drawback to the treatment lies in the bladder and gastro-intestinal irritation sometimes occasioned by the use of such remedies.

About a year ago the attention of Clark, in the Mayo Clinic, was called to the fact that the urine of patients in diabetic coma and that of patients undergoing the ketogenic treatment of epilepsy could be allowed to stand for a very long time without becoming putrid. He explained this phenomenon by supposing that organisms did not grow successfully in a urine whose pH had been greatly lowered by its high content of organic acids, or that some natural urinary antiseptic might exist among the excreted ketones. Acting on this supposition, he subjected a number of his patients with chronic urinary infections to ketogenic diets, and published some highly satisfactory results [1]. The subject was recently briefly reviewed by Cabot [2].

Through the kindness of Professor Murray Lyon we have been permitted to study the effects of such diets on a small number of cases of chronic urinary trouble, which had previously been examined in the urological theatre, and had proved quite resistant to ordinary forms of treatment. The urine from such patients when under treatment, and therefore rich in ketones, was sent to Mr. Lawson Dick (Pharmacological Department), who has studed its inhibiting effect on the growth of *B. coli* in vitro.

SPECIMEN KETOGENIC DIET.

Carbohydrate: 30 grm. Protein: 54 grm. Fat: 251 grm.

Total calories, 2,595.

Total glucose, 86. Fatty acid, 251. G : FA = 1 : 3

Breakfast ...	45 grm. bacon (uncooked weight). Use all bacon fat. 60 grm. tomato, or mushroom. One soy bun. Tea or black coffee with 45 grm. single cream.
Dinner ...	45 grm. lean meat. 90 grm. cauliflower, *or* sprouts, *or* cabbage, *or* spinach. Orange cream (orange juice, 60 grm; double cream, 45 grm.; gelatine, 2 grm.).
Tea ...	60 grm. salad made from lettuce, tomato, cucumber, cress. One soy bun with butter from ration. Tea with 45 grm. single cream.
Supper ...	One egg scrambled with 30 grm. double cream and butter. 90 grm. rhubarb, or vegetable as at dinner. One soy bun with butter from ration. Tea or black coffee with 45 grm. single cream.

Daily Ration: Olive oil ... ... 15 grm. t.i.d
Butter ... ... 97·5 „

The diet used contains a minimum quantity of carbohydrate, a small quantity of protein—since glucose can be formed from protein—and a maximum quantity of fat, so that the glucose/fatty-acid ratio is about 1 : 3. Such a diet is usually capable of producing a marked ketonuria in the adult, though some require the daily intake of carbohydrate to be reduced as low as 20 or even 15 grm. before a satisfactory ketonuria is attained. When it is remembered that a normal diet contains about 300 grm. of carbohydrate it will readily be understood that this is rather a difficult type of diet for the patient to tolerate. On the other hand, in children a ketonuria may be achieved by a much less drastic curtailment of carbohydrate.

All the cases studied had had urinary trouble of some kind or another for years, and had previously been subjected to hospital treatment with unsuccessful results. Every case was examined cystoscopically before and after treatment. Before starting dietetic treatment each case was subjected to a control period on an ordinary diet so that the beneficial effect of hospitalization should not be credited to the ketogenic diet. During this control period the urinary infection of one case, which had previously resisted every effort at treatment for five years, subsided, the urine remaining sterile for the remainder of a long stay in hospital—a significant lesson in the necessity for caution in attributing improvement to a therapeutic procedure. While receiving the standard diet the average pH of the urine, the alkali reserve of the blood—as measured by its carbon dioxide combining power—and the average daily frequency of micturition were determined.

When the effect of hospitalization had worn off and standard conditions had been established, the patients were given a ketogenic diet, beginning with one containing 30 grm. of carbohydrate and having a glucose/fatty-acid ratio of 1 : 3, such as has been described above. The amount of carbohydrate was varied thereafter according to the patient's response. If a strong ketonuria was not obtained, the carbohydrate was reduced by 5 grm. at a time every few days, until

the desired effect was secured. If, on the other hand, vomiting occurred, the carbohydrate was raised by 5 grm. a day until this ceased. The ideal aimed at was the production of the maximum concentration of ketones in the urine without inducing nausea. With this object in view, and in accordance with Cabot's advice, the patient's fluid intake was restricted to approximately 1,400 c.c. a day, the treatment differing in this respect from the ordinary treatment of urinary infections.

It will be seen that the urine in Cases I to V became sterile as the result of these measures, in periods of time varying from three to fifteen days after the onset of the

	Duration of illness before ketogenic treatment	Condition of urinary tract on admission	Organisms	Number of days on diet till no growth on culture	Average pH of urine before treatment (highest)
I	5 years	Cystitis	Streptococci Diphtheroids	5	8·1 (8·5)
II	7 years	Bilateral pyelocystitis	*B. coli*	15	6·0 (6·5
III	3 years	Pyelitis	*B. coli*	14	6·4 (6·5)
IV	8 years	Cystitis	*B. coli*	12	6·8 (7·5)
V	11 years	Bilateral pyelitis	*B. coli*	3	7·8 (8·0)
VI	5 years	Bilateral pyelocystitis	*B. coli* *Staph. aureus*	—	8·0 (8·5)
VII	2 years	Cystitis	*B. coli* *Micrococci tetragenus*	—	6·5 (6·5)
VIII	2 years	Cystitis	*B. coli* *Streptococci*	—	6·5 (—)
IX	1 years	Pyelocystitis	*B. coli*	—	— (—)
X	3 years	Cystitis	*B. coli*	—	7·0 (7·3)
XI	2 years	T.B. kidney and bladder	Tubercle bacilli	—	7·8 (8·0)
XII	7 years	Ureteral spasm	—	—	7·8 (8·5)
XIII	5 years	Trigonitis	—	—	6·5 (7·0)

ketonuria. In each case the treatment was continued for a considerable time after sterility had been established, resulting in the complete disappearance of grossly pathological cystoscopic appearances. In Case I, for example, a small contracted bladder, with thickened, shaggy walls, containing numerous diverticula, returned to normal appearance and capacity after two months in hospital, during which time she had had ketonuria for thirty-five days.

These successful results can hardly be attributed in their entirety to the simple sterilizing effect of urinary hyperacidity. It will be seen that the ketogenic treatment effected a considerable increase of acidity in every case, but in Case IV,

and certainly in Case I, a pH was never attained which was sufficient in itself to account for the antiseptic effect produced. Though the hyperacidity produced in the urine may be the most important curative factor, one cannot help thinking that, in addition, a natural urinary antiseptic exists among the excreted ketones.

In Case VI a marked degree of renal deficiency existed, the result of long-continued backward pressure, and in this case the ketogenic treatment brought about a state of true acidosis, the alkali reserve of the blood, as measured by its carbon-dioxide combining power, being reduced to 50 volumes per cent. In consequence, the treatment

Average pH attained under treatment (lowest)	CO_2 comb. power of blood before treatment (lowest attained by treatment)	Average frequency before treatment (average after treatment)	Length of time between treatment and last report	Remarks and result
6·9 (6·5)	74 (65)	10 (5)	6 months	Very well. No symptoms. No infection.
4·9 (4·8)	67 (59)	6 (4)	3 months	Very well. No symptoms. No infection.
5·2 (4·8)	69 (65)	5 (3)	4 months	Very well. No symptoms. No infection.
6·0 (5·0)	67 (55)	6 (5)	3 months	Very well. No symptoms. No infection.
5·3 (4·8)	65 (59)	11 (8)	2 months	Very well. No symptoms. No infection.
7·5 (7·5)	58 (50)	6 (6)	—	Marked renal deficiency. Treatment discontinued after no apparent effect.
6·2 (5·5)	64 (62)	19 (6)	7 months	Symptoms recurred after discontinuance of treatment.
6·0 (–)	– (–)	18 (12)	—	Vomiting before satisfactory ketonuria. Treatment stopped.
– (–)	– (–)	– (–)	—	No effect after 3 weeks ketonuria. Failure.
– (–)	68 (–)	13 (–)	—	Refractory to diet after two days. Treatment stopped.
6·1 (6·0)	61 (64)	18 (15)	—	No effect. Failure.
5·5 (5·0)	69 (59)	5 (4)	3 months	Pain disappeared during treatment. Recurred later during subsequent pregnancy.
5·5 (4·8)	60 (56)	24 (6)	1 month	Complete recovery.

had to be discontinued, but it is only fair to point out that it had already been given a fair trial and had produced no noticeable effect on the infection. All the other cases had a satisfactory kidney function, as demonstrated by renal efficiency tests, and in these the treatment produced no serious fall in the alkali reserve. This corresponds with our experience in treating epileptic cases with ketogenic diets. It would appear, therefore, that as long as the kidneys are efficient they will have no difficulty in maintaining the acid-base balance of the blood, even under prolonged ketogenic treatment, but when the renal efficiency tests indicate an impaired function the treatment should be given with great caution, if at all.

Case VII had a long period of treatment, but complete sterility of the urine was never established, though the infection was considerably reduced. In addition, there was great improvement in the cystoscopic appearances, and it will be seen that the frequency of micturition was markedly alleviated. A reduction in the frequency was, indeed, noticed in every case. In some this may be explained by the slight curtailment of fluids and by the effect of prolonged hospitalization. In Cases VII and XIII, however, the improvement seems too striking to be accounted for so simply. It is, at any rate, apparent that urine made acid by an induced ketonuria does not have the irritating effect of urine made acid by other measures.

Cases VIII to XI must be accounted failures. In Case VIII vomiting always occurred before a satisfactory ketonuria could be established, and the attempt to produce it had to be abandoned. Case IX was a child, treated by Dr. Wallace in the Sick Children's Hospital, and he has kindly permitted me to include the result. After three weeks strong ketonuria, easily induced as is usual in children, the urinary infection was as severe as ever. Case X revolted with expletives against his diet on the second day, through pique rather than through nausea. It is apparent that patients will be encountered not infrequently who will refuse to drink their bacon fat or to eat mushrooms cooked in cream, and I have, therefore, included Case X as an example. Case XI had a tuberculous kidney and bladder, and the treatment was not unexpectedly inefficient in dealing with the highly resistant acid-fast bacillus.

Cases XII and XIII were suffering from attacks of ureteral spasm and severe trigonitis respectively. In Case XII the patient had no attacks of pain while under treatment, but this may have been pure coincidence, for they recurred when she went home. Case XIII was brilliantly successful. For years, in spite, of every sort of treatment, the patient's life had been a misery to her owing to a constant desire to pass water. The frequency began to improve shortly after ketonuria was established, and in a fortnight she was passing water quite normally. The improvement was so dramatic that one had to consider the possibility of suggestion having been the prime factor in effecting the result. This is, however, unlikely as the patient had previously been subjected in hospital to much more striking therapeutic measures without improvement, and in addition there was no other patient in the ward at the time who was benefiting from the treatment.

Several other cases have been treated by the ketogenic treatment, but these have not been included, as they were not rigidly controlled. As the result of observation on these cases, however, there can be little doubt that in certain local inflammatory or irritative conditions of the urinary tract a ketonuria exercises a sedative and analgesic action.

To sum up: Out of eleven cases of very chronic and intractable urinary infection, five were apparently cured by the treatment, and one was considerably benefited. In one case of trigonitis with marked frequency the symptoms entirely subsided. Three patients were refractory to the diet for various reasons, and the treatment, which had not so far proved successful, had to be discontinued. In two cases the diet was given a fair trial and proved quite ineffective, but in one of these the patient was suffering from a tuberculous infection. It is possible that the results would have been better if the dietetic treatment had been combined with the administration of an acid-producing salt like ammonium nitrate, as is recommended by Clark. In this way the urinary acidity can be greatly increased. One was anxious, however, to try-out the effect of the diet alone, uncomplicated by other treatment.

To my mind the interest of this investigation lies in the bacteriological results about to be described by Mr. Lawson Dick, rather than in the somewhat limited clinical results.

While we believe that there is a future for this type of diet in the treatment of these unfortunate and intractable cases, it is highly important that its limitations should be understood. It lacks universality of application, since it is a somewhat

specialized method of treatment, and is quite unsuitable for very sick or pyrexic patients. It requires a competent dietitian, careful supervision of cooking, constant clinical observation of the patient and, ideally, laboratory control of the case. It is difficult, therefore, for out-patients, and requires special facilities even in hospital. Even then, it is not apparently always successful. Again, the diet is an expensive one, and in adults a ketonuria is often exceedingly difficult to attain without the most drastic restriction of carbohydrates, so that nausea and vomiting may precede the ketonuria, requiring the diet to be stopped. It is not, therefore, the philosopher's stone of treatment, but may be used when other methods have failed, and may, on occasion, be dramatically successful.

[I am indebted to the Medical Research Council for a part-time grant.]

References.—[1] HELMHOLTZ and CLARK, *Proc. Staff Meetings, Mayo Clinic*, 1931, vi, 605-609. [2] CABOT, *Lancet*, 1931, (i) 1038-1040.

(III) Mr. I. Lawson Dick.

The objects of the researches to be described were:—

(1) To measure the bactericidal or bacteriostatic properties of urine passed by patients in a state of ketosis.

(2) To determine whether these properties are due to changes caused by diet in the reaction of the urine, or to some unknown antiseptic substance.

That the disinfectant action of mineral acids is proportional to their degree of dissociation was shown by Kronig and Paul in 1897. Since then it has been shown that their disinfectant action is, in general, directly proportional to the pH or true acidity of their solutions, and not to their normal strength or total acidity. For example, Winslow and Lochridge found that, in the case of hydrochloric and sulphuric acids, their disinfectant action was in proportion to their degree of dissociation in solution. This they did by showing that a 100% destruction of *B. coli* was effected in forty minutes by 0·0123 N HCl, while 0·0166 N H_2SO_4 was required to produce the same result in the same time. The solution of H_2SO_4 is apparently appreciably the stronger, but because the HCl is the more fully dissociated the pH or true acidity of these solutions is the same. The pH or true acidity and not the total acidity is therefore the important factor in regulating bacterial growth in the urine.

Methods.—In the present experiments measurements of the pH of the urine were made by an indicator method, using a Hallige comparator. The indicators used were: Methyl red, pH 4·4 to 6·0; chlorphenol red, pH 5·2 to 6·8; bromthymol blue, pH 6·2 to 7·6; cresol red, pH 7·2 to 8·8.

When it was required to change the pH of a sample of urine the necessary alteration was made by the addition to the urine of the appropriate amount of decinormal HCl and NaOH. This acid and this alkali were chosen because, while they altered the reaction of the urine, they did not introduce any ion which was not already present in abundance.

The organism whose behaviour under the various conditions was studied was the commonest invader of the urinary tract, the *B. coli*. A pure growth of typical *B. coli* was isolated from the urine of a young adult suffering from acute pyelitis. It gave the following typical biochemical reactions:

Glucose	Lactose	Dulcite	Saccharose	Adonite	Inosite	Indol production	Liquefaction of gelatin
+	+	+	−	−	−	+ve	−ve

(+ = fermentation of sugar with production of acid and gas. − = no fermentation.)

The method was to inoculate a standard number of *B. coli* into sterile urine of known pH, and to record the growth of the organisms over five hours incubation. Some preliminary experiments were carried out in order to determine what would be a suitable standard original inoculum, and the following was selected. A twenty-four-hours agar slope culture of *B. coli* was emulsified in a few c.c. of sterile saline. This emulsion was diluted until it was of an opacity equal with Brown's opacity tube No. 8. 1 c.c. of this emulsion was then subjected to two decimal dilutions, and it was found that if one 3 mm. loopful of this final emulsion was added to 50 c.c. of urine, the urine then contained roughly 100 organisms per c.c., which was a convenient original inoculum for all subsequent experiments.

The pH of the urine was adjusted to the desired figures of 4·8 and 5·5 by the addition to the urines of hydrochloric acid or NaOH. The urine was passed through a Seitz filter of "medium" porosity. This method of sterilization was adopted because it did not in any way alter the chemical or physical properties of the urine. 50 c.c. of this sterilized urine was transferred by means of a sterile pipette to a sterile conical flask. 1 c.c. of the urine from this flask was added to melted agar, plated, and the plate incubated, as a control of the sterilization. These agar controls were sterile in every experiment recorded.

Each of the flasks of urine was inoculated with one 3 mm. loopful of the previously specified emulsion of *B. coli*. 1 c.c. of this inoculated urine was pipetted into melted McConkey's medium in order to determine the exact number of this original inoculum. The flasks were incubated at 37° C., and 1 c.c. of the urine was similarly plated after five hours incubation. It was sometimes found necessary to dilute the urine during plating at this time, otherwise the colonies would have been so numerous as to be uncountable. These plates were incubated for twenty-four hours, and the colonies were enumerated.

Results.—In order to make the results directly comparable the original inoculum was taken in every case as 100 organisms per c.c., and the five hours figure was corrected to terms of that number.

Table I shows the results of twenty-four experiments carried out in that manner, with the urine from twelve patients confined to hospital because of some simple surgical condition, such as fracture of the leg, but who were otherwise healthy adults. In each case two specimens of urine were examined, one at pH 4·8 and the other at pH 5·5. In no case was there any free growth of *B. coli* in urine at a pH of 4·8. In two cases (H. M. and C. S.) there was some slight increase at the end of five hours' incubation, but neither of these increases is quite outside the margin of experimental error. In the remaining ten cases there is a great reduction in the number of organisms, amounting in four cases to complete sterilization. The average number of colonies after five hours' incubation at pH 4·8 was twenty-eight per c.c. In all of the twelve sterilization was produced by the end of twenty-four hours.

At pH 5·5 the organisms grew luxuriantly in all but two cases. In one of these (H. C.) sterilization was produced at the end of five hours. In the other (C. S.) growth was arrested for five hours, but was luxuriant at the end of twenty-four hours, as it was in the remaining ten cases. The average number of colonies, after five hours incubation at pH 5·5, was 11,636 per c.c. Thus it would appear that while free growth of *B. coli* can occur in urine at pH 5·5, an increase of acidity to pH 4·8 inhibits the growth entirely. Dr. Dunlop has shown that this degree of acidity can sometimes be reached in ketonuria.

Tables II and III show the effect of ketonuria on the growth of *B. coli* in the urine. In Table II appear four specimens of unknown pH and twelve of pH more acid than 5·5. Table III contains seventeen experiments in which the pH was 5·5, or more alkaline. The results in Tables II and III can be summarized as follows: Thirty-three measurements of bacterial growth were made on the urines of four patients

who were receiving a ketogenic diet. In a large number of specimens no growth of *B. coli* occurred in five hours, and in no case was there free growth. The urine in these cases therefore contains some factor which hinders bacterial growth. The question at once arises whether this factor is simply increased acidity. The averages of the results shown in the three tables can be compared as follows:—

	No. of specimens	Average colonies per c.c. after 5 hours. (Inoculum 100 per c.c.)
Normal urine at pH 5·5	12	11,636
Ketogenic urine, pH unknown	4	90
Ketogenic urine, pH more acid than 5·5 ...	12	130
Ketogenic urine, pH 5·5, or more alkaline ...	17	304

This analysis shows that the power of ketogenic urines to inhibit bacterial growth is nearly as great when the pH is more alkaline than 5·5, as when it is more acid than 5·5. In both cases the growth is far less than that which occurs in normal urine at pH 5·5.

I conclude therefore that the bacteriostatic properties of ketogenic urine cannot be accounted for solely by changes in the reaction of the urine, but must also be due to some unknown substance. The number of cases investigated is admittedly small, and it is hoped to repeat this work on a more extensive series.

I wish to thank Professor Clark and Professor Mackie for their assistance and advice in this research.

TABLE I.—EFFECT OF ALTERATION OF PH ON GROWTH OF *B. coli* IN URINE.

Name	pH	Inoculum per c.c.	No. of colonies per c.c. at 5 hours	Growth at 24 hours
H. M. ...	4·8 ...	100 ...	147 ..	–
R. H. ...	4·8 ...	100 ...	0 ...	–
A. B. ...	4·8 ...	100 ...	39 ...	–
J. J. ...	4·8 ...	100 ...	0 ...	–
A. C. ...	4·8 ...	100 ...	5 ...	–
H. C. ...	4·8 ...	100 ...	0 ...	–
R. K. ...	4·8 ...	100 ...	5 ...	–
S. S. ...	4·8 ..	100 ...	2 ...	–
J. S. ...	4·8 ...	100 ...	0 ...	–
C. S. ...	4·8 ...	100 ...	137 ...	–
J. I. ...	4·8 ...	100 ...	13 ...	–
M. M. ...	4·8 ...	100 ...	3 ...	–
Average number of colonies after 5 hours' incubation at pH 4·8, 28				
H. M. ...	5·5 ...	100 ...	17,710 ...	+
R. H. ...	5·5 ...	100 ...	15,540 ...	+
A. B. ...	5·5 ...	100 ...	23,300 ...	+
J. J. ...	5·5 ...	100 ...	18,900 ...	+
A. C. ...	5·5 ...	100 ...	4,340 ...	+
H. C. ...	5·5 ...	100 ...	0 ...	–
R. K. ...	5·5 ...	100 ...	18,820 ...	+
S. S. ...	5·5 ...	100 ...	1,700 ...	+
J. S. ...	5·5 ...	100 ...	8,150 ...	+
C. S. ...	5·5 ...	100 ...	119 ...	+
J. I. ...	5·5 ...	100 ...	27,750 ...	+
M. M. ...	5·5 ...	100 ...	3,300 ...	+
Average number of colonies after 5 hours' incubation at pH 5·5, 11,636				

TABLE II.—GROWTH OF *B. coli* IN KETOGENIC URINES OF pH UNKNOWN OR MORE ACID THAN 5·5.

Name	pH.	Inoculum per c.c.	No. of colonies per c.c. at 5 hours	Growth at 24 hours
A. R.	–	100	91	+
A. R.	–	100	118	+
G. N.	–	100	135	+
G. N.	–	100	15	+
A. R.	5·0	100	194	+
A. R.	5·0	100	77	+
A. R.	5·0	100	88	+
A. R.	5·0	100	280	+
M. H.	5·0	100	202	+
M. H.	5·0	100	112	+
M. H.	5·0	100	156	+
M. H.	5·0	100	133	+
M. H.	5·0	100	0	–
M. H.	5·0	100	77	+
M. R.	5·0	100	85	+
M. H.	5·0	100	157	+

Average number of colonies after 5 hours' incubation (pH unknown) 90.
Average number of colonies after 5 hours' incubation (pH 5·0) 130.

TABLE III.—GROWTH OF *B. coli* IN KETOGENIC URINES OF pH 5·5 OR MORE ALKALINE.

Name	pH	Inoculum per c.c.	No. of colonies per c.c. at 5 hours	Growth at 24 hours
G. F.	5·5	100	38	+
G. F.	5·5	100	230	+
G. F.	5·5	100	793	+
G. F.	6·0	100	76	+
M. H.	6·0	100	590	+
M. H.	6·0	100	533	+
M. H.	6·0	100	359	+
M. H.	6·0	100	344	+
M. H.	7·0	100	112	+
A. R.	7·0	100	7	+
A. R.	7·0	100	546	+
G. N.	7·5	100	447	+
G. N.	7·5	100	157	+
G. N.	7·5	100	344	+
G. N.	7·5	100	46	+
G. N.	8·0	100	266	+
G. N.	8·0	100	282	+

Average number of colonies after 5 hours' incubation (pH 5·5 or more alkaline) 304

Discussion.—Dr. A. Q. WELLS : I hesitate to disagree with Mr. Lawson Dick, owing to the small number of ketogenic urines that I have examined, but, personally, I have found that the urine from patients on a ketogenic diet, provided that the urine contains ketone bodies and has a pH of 5·5 or less, is not only bacteriostatic, but is bactericidal to *B. coli*. I have inoculated two such ketone urines, which were initially sterile, with *B. coli*, and, by means of hourly shake cultures, have enumerated the bacterial content. This content falls rapidly, and within twenty-four hours both specimens were sterile. It would appear that this bactericidal effect is not wholly due either to the acidity of the urine or to the ketone bodies therein. *B. coli* will grow actively in a urine whose pH has been adjusted to 5·0 or slightly lower. I have endeavoured to reproduce a ketone urine by the addition of sodium aceto-acetate to a normal urine so as to give a concentration of 0·4 grm. %. When the pH of such a urine is adjusted to 5·6, the inoculation of *B. coli* leads to active growth. I have found that the pH must be lowered to 4·9 before it becomes bactericidal.

Dr. A. P. CAWADIAS : The valuable communication which we have just heard must not cause us to lose sight of the general physiopathology of an important group of urinary infections and of their complete treatment. Urinary infections with *B. coli* and enterococcus constitute a book in three chapters. The first chapter is intestinal, the second metabolic, and the third urinary. The germs first come out of the intestine because of intestinal

disturbances ; they next develop in the urine, because of metabolic disturbances ; lastly they localize in the urinary tract owing to local disturbances. Therefore treatment of the intestine must come first, as was pointed out twelve years ago by the French surgeon Heitz-Boyer. The ketogenic diet is directed against the metabolic element of alkalosis, and has given remarkable results. I am astonished, however, to hear that this diet has only recently been introduced by American workers. In fact, since 1920, following the work of Heitz-Boyer, Goiffon and others, diet with high protein content, very high fat content and extremely low carbohydrate content under the term of acidifying diet has been the routine method of treatment for *B. coli* and enterococcus infections of the urinary tract. This has probably escaped the notice of the American workers.

Dr. LEONARD FINDLAY: We must all be grateful to the readers of the papers for their comprehensive survey of this interesting question. One is, however, struck by the want of concordance between the experiments *in vivo* and those carried out *in vitro*. In my own experience, clinical tests with this line of treatment, not only in pyuria but also in epilepsy, have been definitely disappointing; I think this is not to be wondered at in view of the life history of therapeutic ketosis.

In the child a severe degree of ketosis is easily induced by the ketogenic diet, as evidenced by the abundant acetone in the urine and the fall in the carbon dioxide content of the blood. Symptoms of acidosis (hyperpnœa and restlessness, etc.) are, however, conspicuous by their absence. Vomiting occasionally occurs but this is almost certainly due to nausea on account of the excessive amounts of fat in the diet and not to any metabolic change. Equally striking with the absence of symptoms in this variety of ketosis is the rapidity with which the patient accommodates himself to the new dietetic conditions, so that within from twenty-four to forty-eight hours the acetonuria diminishes, the pH of the urine, which showed an initial fall, rises and the carbon dioxide content of the blood returns to normal. Thus it would appear that if the state of ketosis is to have any therapeutic effect this must take place during the first twenty-four or forty-eight hours after the institution of the diet.

We have heard to-night the curative effect of the diet ascribed to the consequent acetonuria, and to the lowering pH of the urine, but there is one other factor which should not be forgotten and to which I have heard no reference made this evening. A constant accompaniment of ketosis is diuresis which we recognize as one of the best measures in the treatment of pyuria. I may remark that the latest idea of the beneficial effect of the ketogenic diet in epilepsy is that it is due to dehydration of the tissues consequent on this very factor, and that it is due neither to acetonæmia nor acidosis.

Dr. L. P. GARROD said that the urine of a patient on a sufficiently strict ketogenic diet might completely fail to support the growth of *B. coli*, even when incubated for as long as twenty-four hours after artificial inoculation. The hypothesis of a naturally produced "antiseptic" was not the only possible explanation for this; the deprivation of substances normally promoting growth might have a similar effect. The fact that the growth of *B. coli* was restrained by acidity in urine had been demonstrated several times in the past, and when he (the speaker) had referred to experiments showing this during a joint discussion by this Section and the Sections of Pathology and Therapeutics and Pharmacology in 1929,[1] it had been suggested that a strongly acid urine, however beneficial, was intolerable to the patient with a urinary tract infection. Recent work with the ketogenic diet had shown this objection to be without foundation.

Proceedings, 1929, xxii, 1146 (Joint Discussion No. 6, 91).